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13. ABSTRACT *(Maximum 200 words)*

This five year project will define risk factors associated with breast carcinoma in-situ through the mechanism of a case/control study. The study population consists of approximately 1100-1200 cases of female breast carcinoma in-situ (BCIS) and 1100-1200 age-matched female controls selected from the state of Connecticut. At the end of year four, case and control ascertainment is complete with 1537 eligible cases and 1285 eligible controls identified. Physicians have consented for 91% of eligible cases. Eighty-seven percent of contacted eligible cases and 85% of contacted eligible controls have agreed to participate in telephone interviews which collect information concerning family history of cancer, pregnancy and menstrual history, hormone replacement therapy, oral contraceptive use, fertility drug use, as well as sociodemographic variables. Preliminary analyses suggest that many of the risk factors traditionally associated with invasive breast cancer, including a family history of breast cancer, are also associated with the development of BCIS. In addition to the interview portion of the study, which is now essentially complete, the expression of p53, c-erbB-2 as well as estrogen and progesterone receptors will be examined in paraffin-blocks from a subset of cases.

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PI - Signature Date

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THE GENETIC EPIDEMIOLOGY OF BREAST CARCINOMA IN SITU

5. INTRODUCTION

Breast cancer remains one of the most important health care issues of the 20th century. Despite a wealth of studies on the topic, the current literature provides little information regarding the nature of the epidemiologic risk factors or clinical characteristics of breast tumors which are classified as non-invasive, i.e., breast carcinoma in situ (BCIS). As screening efforts throughout the United States have increased, so has the number of women diagnosed with BCIS, with up to 20% of screened patients diagnosed with this lesion. The identification of risk factors associated with the development of BCIS is especially important, particularly in light of the fact that in the coming century up to one in fifty women in the United States will be diagnosed with this tumor during her lifetime. This five-year project will define risk factors associated with BCIS through the mechanism of a case/control study. The study population will include approximately 1100-1200 cases of female breast carcinoma in situ and 1100-1200 age-matched female controls selected from the population of the state of Connecticut over a 3.5 year data collection period. Cases will be between the age of 20 and 84 years at time of diagnosis. The controls will be frequency matched to the cases by five year age intervals. Telephone interviews will be conducted with the study subjects and will collect information concerning family history of cancer, pregnancy and menstrual history, hormone replacement therapy, oral contraceptive use, fertility drug use, as well as sociodemographic variables. In addition, a tissue repository consisting of paraffin-embedded tumor tissue collected from a subset of the cases will be formed. The expression of two of the most frequently reported oncogenes associated with invasive breast cancer, p53 and c-erbB-2, will be examined in these BCIS cases for the first time in a population-based series.

The goals of this study are as follows:

1. To determine whether there is an association between a family history of breast and/or ovarian cancer and the development of breast carcinoma in situ (BCIS).

2. To determine whether there is an association between additional epidemiologic risk factors, including those traditionally associated with invasive breast carcinoma such as age at menarche, age at first birth, and oral contraceptive use and the development of BCIS.

3. To collect paraffin-embedded tumor tissue for a subset of the BCIS cases.

4. To test for the presence of p53 and c-erbB-2 protein expression as well as estrogen and progesterone receptor expression using the methods of immunohistochemistry in the paraffin-embedded tumor tissue.

5. To examine the association between p53, ER, PR and/or c-erbB-2 expression in BCIS tumors with clinical and epidemiologic variables including grade and family history of breast cancer.

6. To develop risk prediction models to be used in defining screening guidelines for women not yet diagnosed with BCIS.

Specific Location of Study

Drs. Claus and Holford have offices located in the Department of Epidemiology and Public Health. Drs. Carter and Badve have office and laboratory located within the Pathology Department. The office of Dr. Meredith Stowe, Project Director, and Ms. Judie Fine, Director, Rapid Case Ascertainment Shared Resource, is located at 200 College Street, New Haven, CT.

6. BODY

RESEARCH PLAN

The cases are ascertained through the Rapid Case Ascertainment (RCA) Shared Resource of the Yale Cancer Center, under the direction of Ms. Judie Fine. The physicians of each eligible case are identified by Ms. Fine. The names of patients and physicians are given to Dr. Meredith Stowe, the project director, by Ms. Fine. A letter signed by Drs. Claus and Stowe is sent to the physicians requesting permission to send a letter of introduction to the case.

Proto-controls are identified by Northeast Research in Orono, Maine through the mechanism of random-digit dialing. Female residents of the state of Connecticut aged 20-84 who are served by a telephone are eligible.

Those cases approved for contact by their physicians are sent a letter of introduction from Drs. Claus and Stowe explaining the project. Controls receive a similar letter. Informed consent forms accompany the letter of introduction and study subjects are asked to return them via the stamped, addressed envelope provided. Approximately 1-2 weeks later an interviewer (either Ms.

Sheila Griffin or Ms. Marjorie Jasmin) contacts the potential study subject by telephone. If the potential study subject decides to participate, the interviewer administers the questionnaire over the telephone at the patient's convenience after verbal consent has been given for the interview. Subjects who agree to be interviewed are sent an oral contraceptive picture booklet with an accompanying letter. Subjects are interviewed for approximately 30-45 minutes. Interviews of women with particularly complex family or medical histories may take somewhat longer. The questionnaire includes questions on family history of cancer, pregnancy and menstrual history, oral contraceptive and other exogenous hormone history, medical history, socioeconomic status, as well as alcohol and tobacco use.

We plan to collect pathology slides and histologic specimens in the form of paraffin-embedded tumor tissue. Cases who agree to allow us to retrieve paraffin-embedded blocks are sent an authorization of health information form which we ask them to return via mail. RCA will request and courier slides and paraffin-blocks from each of the pathology departments as well as return the slides and blocks after the laboratory analyses are completed. The blocks are returned to the various hospitals after sufficient material has been removed from them. Alternatively, hospitals may choose to cut material from the blocks rather than send the block itself. The slides will be quickly returned after our pathologist, Dr. Darryl Carter, has reviewed them to confirm the diagnosis and perform a uniform histologic review.

Medical records may need to be reviewed to provide details requested in the questionnaire regarding dates of diagnoses or pathologic details of diagnosis. In particular, pathology data are useful in identifying tumor blocks most likely to contain tumor. A stamped, addressed envelope is provided for study subjects so that they may return the authorization for release of health information (for review of medical records and retrieval of paraffin-blocks) via mail. Dr Stowe telephones study participants who do not return the form to encourage them to do so. Replacement forms are sent to women who misplace the original form.

YEARLY REPORT

The personnel on the project has remained stable, with Drs. Claus and Holford continuing to act as Principal Investigator and Co-Investigator, respectively. Dr. Meredith Stowe continues as the project director while our two interviewers, Ms. Sheila Griffin and Ms. Marjorie Jasmin, continue to work with us (although at a much reduced rate as the last few interviews are completed) and Ms. Judie Fine remains as the director of the Rapid Case Ascertainment Service. Dr. Darryl Carter continues as our senior pathologist. In addition, we have been lucky enough to hire an additional pathologist, Dr. Sunil Badve, with extensive expertise in breast carcinoma in-situ (see attached c.v. and sample manuscript), who with Dr. Carter will provide uniform review of slides for cases as well as serve as the primary pathologist for the immunohistochemical studies. The addition of Dr. Badve to the study assures that the laboratory goals of the study are

attained in a timely fashion (necessary due to the greater than expected numbers of cases and our high response rate.)

The goals of year four included 1) the continued identification (through March 1998), consent, and interview of cases and controls, 2) continued uniform histologic review of slides for each case, 3) identification and accession of paraffin blocks, and 4) preliminary data/statistical analyses. The details of case and control ascertainment are presented in Table 1. At this point in time, 1738 cases have been identified for the study through the services of the Rapid Case Ascertainment Service (Case ascertainment is now closed). One thousand five hundred and thirty-seven of these cases have been verified to be eligible, 189 to be ineligible, and 12 are pending eligibility review. One thousand three hundred and five controls have been identified by Northeast Research, 1285 of whom remain as verified controls. Given our initial sample size estimate of 800 cases and 800 controls, we have surpassed our study goals with respect to sample size.

Our physician consent rate for cases has remained high with 91% of cases having a consenting physician. This represents a slight decrease from our previous number (94%) and is primarily due to changes in the consent procedures at two hospitals (Mt. Sinai and St. Francis Hospitals). At both of these hospitals, no case subject may be approached by a study prior to that case 1) being approached by the consenting physician and 2) having the study explained by that physician. As can be imagined, although the majority of these physicians verbally agree to contact the women, none of the cases at these two hospitals have actually been contacted by these physicians due to restraints of time and personnel on the part of these physicians. This has proved a difficult problem to overcome despite continued negotiations with the hospitals.

Once we are able to approach the study subjects, our case and control response rates remain high; among eligible cases who have been contacted by our study, 87% have agreed to participate in the interview portion of the study. Among eligible controls who have been contacted by our study, 85% have agreed to participate in the interview portion of the study.

In addition to the interview portion of the study, we continued upon the histologic slide/ paraffin block collection portion of the study. This portion entails obtaining written permission from cases to retrieve the slides/blocks and then physical retrieval of this material from hospitals for review/laboratory analysis. At present, only two percent of interviewed cases have actively refused to allow us to retrieve slides/blocks. The remainder have verbally agreed to allow us to retrieve slides and blocks. Approximately 84% of interviewed cases have given written consent for retrieval of histologic slides while 74% of interviewed cases have given written consent for paraffin-block retrieval (note that the difference between the two numbers indicate the women who did not wish laboratory testing performed on their tumors). As in the past, we are mailing additional permission forms and retelephoning women regarding the permission form to raise our written consent levels (necessary for actual retrieval to occur) for this portion of the study. Once written permission to retrieve pathology slides has been obtained, Ms. Fine requests the slides

from the various hospitals. We have had good success with obtaining slides for review with no refusals from hospitals at present although in some instances we have had to travel to the hospital to review slides. Both Drs. Carter/Badve then review all of the slides for diagnosis and select blocks for retrieval and laboratory analysis.

We are also continuing to retrieve blocks for those women who have given permission. Interestingly enough, we have had less difficulty than expected in retrieving paraffin blocks from the various hospitals as a number of hospitals who had initially refused to send us blocks now have agreed to send the blocks. Of note, we have decided to select the Dako HER-2 monoclonal antibody for erbB-2 staining. These particular antibodies were selected as they are the ones used most frequently in clinical practice (the Dako product will be the stain used to determine positivity for the newly FDA approved Herceptin use), hence they would be most relevant to data that is currently collected and used clinically in women diagnosed with invasive carcinoma of the breast.

Our pilot data/preliminary immunohistochemical staining (n=219) results indicate that overexpression of ER, PR, and HER-2/neu occurred in approximately 60%, 62% and 30% of cases, respectively. HER-2/neu expression was correlated with higher grade, was most frequent in comedocarcinoma, and was inversely correlated with both ER and PR. This are extremely interesting findings given the associations reported in invasive breast cancer cases, i.e. that ER+ tumors are associated with increased survival time while HER-2/neu+ or comedo tumors are associated with lesser survival time.

Data entry for the study is ongoing and is completed by Ms. Wanda Carr. At present a total of 924 case interviews and 1010 control interviews have been entered and error checked.

Data analysis continued this year and two manuscripts are in preparation: "The epidemiology of breast carcinoma in-situ" and "Family history and the risk of breast carcinoma-in situ".

The interview portion of the study is essentially complete. In the coming year, we will finish the slide review and focus on the laboratory portion of the study. Data analysis and manuscript preparation will be ongoing as the final data are collected and prepared for analysis.

HUMAN SUBJECTS

Subject Population

All female Connecticut residents between the ages of 20 and 84 years at time of diagnosis and diagnosed with breast carcinoma in situ from 9/15/94 to 3/14/98 are eligible. Cases with a previous history of breast cancer and/or a breast biopsy of unknown outcome are excluded. In this time period, 1738 women were diagnosed with BCIS in the state of Connecticut within the age-group of interest. From this group, we expect to interview approximately 1100 women. Proto-

controls were randomly selected by an external firm (Northeast Research) and consist of age-matched Connecticut female residents. We identified 1305 proto-controls and expect to interview approximately 1100 as controls.

Risks/Benefits

As this is primarily an interview study, we anticipate no physical risk to study subjects. However, given the serious nature of breast cancer, it is conceivable that some patients will experience some degree of psychological distress as a result of being interviewed concerning their health status. In order to minimize the occurrence of such distress, interviewers are trained to conduct interviews in a relaxed, friendly, and professional manner. Swift corrective action will be taken concerning any interviewer whose demeanor seems to have a negative effect on study participants.

There are no monetary inducements to participants in this study. The primary inducement for participants is the ability of the study to contribute to our understanding of breast cancer. This research has the potential to define modifiable risk factors associated with the development of breast cancer as well as the potential to identify currently healthy women at increased risk of this disease who might benefit from increased screening for breast cancer.

At present no adverse effects have been reported in this study. A number of positive effects have been reported, particularly to our interviewers, including the improvement of family relationships in association with the gathering of family history information. In addition, among cases, the discussion of a breast cancer diagnosis with an independent observer has proved to be helpful to a number of women.

Protection of Subjects

Each study subject is assigned a code number. The interview cover sheet containing identifying information is removed from the interview booklet and stored separately. All staff members are informed prior to employment and at regular intervals as to the necessity for keeping all data confidential. All written study material is stored in locked file cabinets. All histologic specimens will be stored in the laboratory of Dr. Carter.

The opinion of Dr. Carter, the study pathologist, concerning histologic specimens may in some instances differ from that of the original pathologist. If Dr. Carter interprets the woman's cancer to be invasive rather than solely in-situ, the original pathologist and surgeon will be contacted and informed of the opinion of the study pathologist. If the original pathologist is not available, we will inform the Chair of Pathology at the appropriate hospital.

No information that identifies an individual subject will be given to third parties, including family members, unless that subject has given consent to do so. Information obtained during the study will not be placed in a subject's medical record. Publication and presentation of results will contain only aggregate data.

No laboratory test results on specimens will be released to the participant or her physician. This current work is in the realm of research and any results should be regarded as preliminary findings and not definitive. None of the materials collected on these patients will be used to do research unrelated to their breast cancer diagnosis.

Human Investigation Committee Approvals

We have had great success in obtaining the approval and participation of the state's hospitals. At present, all but four of the state's 35 hospitals are active participants. We are able to identify cases diagnosed and treated at these four hospitals via the Connecticut Tumor Registry. Overall, the response of the state's hospitals and medical personnel has been extremely positive. Most of the hospitals are now in their four year of participation with our study.

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SUMMARY OF SUBJECTS' PARTICIPATION

November 15, 1994 - November 14, 1998

	CASES	CONTROLS
IDENTIFIED	1738	1305
ELIGIBILITY		
Verified Eligible	1537	1285
Verified Ineligible	189	20
Pending	12	---
Ineligible due to:		
language	*13*	*17*
residency(not CT)	*5*	*3*
previous breast cancer	*71*	
not BCIS	*100*	
MD CONSENT TO CONTACT		
Yes	1245	---
No	125	---
Pending	145	---
INTERVIEW STATUS		
Interview Completed	1045	1045
Interview Scheduled	3	1
Interview Refused	144	190
Pending	35	22
Deceased	2	0
Incompetent/too ill	7	4
Hearing problem	0	1
Unable to contact	9	22
DATA ENTRY STATUS		
Pending	121	35
Completed	924	1010
PATHOLOGY		
Releases: slide review: 880 path. specimen: 774	Slides obtained: 467	Reviewed: 376

Prediction of Local Recurrence of Ductal Carcinoma *In Situ* of the Breast Using Five Histological Classifications: A Comparative Study With Long Follow-Up

SUNIL BADVE, MRCPATH, ROGER P. A'HERN, MSA, ANN M. WARD, MA, ROSEMARY R. MILLIS, FRCPATH, SARAH E. PINDER, MRCPATH, IAN O. ELLIS, MRCPATH, BARRY A. GUSTERSON, FRCPATH, AND JOHN P. SLOANE, FRCPATH

The increased detection of ductal carcinoma in situ (DCIS) by mammographic screening and the more widespread use of breast-conserving surgery have led to a search for histological features associated with the risk of recurrence. In a case control study of 141 patients with long follow-up, we compared the ability of five morphological classifications to predict recurrence after local excision. A significant correlation was not found between recurrence and growth pattern when a traditional classification based on architecture was used nor with necrosis when a scheme based principally on this feature was employed. A correlation was, however, found between recurrence and "differentiation" as defined by nuclear features and cell polarization in a classification recently formulated by the European Pathologists Working Group (EPWG), but this failed to reach statistical significance at the 5% level. A stronger and statistically significant correlation was found between nuclear grade as defined by the EPWG and recurrence when cell polarization was disregarded, using the classification currently employed by the UK National Health Service and European Commission–funded Breast Screening Programmes. This was attributable to a small number of recurring cases being downgraded as a consequence of exhibiting polarized cells. A significant correlation between histology and recurrence was also observed using the Van Nuys classification, which is based on nuclear grade and necrosis. Whether the tumor recurred as in situ or invasive carcinoma was unrelated to histological classification, as was the time course over which it occurred. These findings strongly support the use of nuclear grade to identify cases of DCIS at high risk of recurrence after local excision, but further work is necessary to determine whether nuclear grade or necrosis is more appropriate to subdivide the non–high-grade cases. HUM PATHOL 29:915-923. Copyright © 1998 by W.B. Saunders Company

Key words: **breast, ductal carcinoma in situ, classification, recurrence.**

Abbreviations: **DCIS, ductal carcinoma in situ; EC, European Commission; EPWG, European Pathologists' Working Group; NHSBSP, National Health Service Breast Screening Programme.**

The frequency with which ductal carcinoma in situ (DCIS) is encountered in biopsy and excision specimens of breast has increased dramatically since the introduction of mammographic screening, accounting for nearly 20% of screen-detected cancers, compared with about 5% of those in symptomatic women in the United Kingdom.[1]

At the same time, there has been an increase in breast-conserving surgery, which although having undoubted cosmetic benefits, runs the risk of not eradicating the disease. It has been estimated that if left untreated, DCIS will develop into invasive carcinoma in a significant proportion of cases, generally within 10 years of diagnosis.[2,3] Local recurrence as in situ or invasive disease after breast-conserving surgery has been reported in 5% to 23% of cases, depending on the choice of adjuvant treatment.[4] Clearly, the most important determinant of recurrence is the adequacy of surgical excision, but pathological assessment of excision margins, although useful, is beset with technical difficulties.

DCIS is not a single morphological entity but a heterogeneous group of proliferations that vary according to cytology and growth pattern. Classification has traditionally been based on the latter, and a number of studies have shown a relationship between this aspect and behavior; comedo carcinomas, for example, have been found to be more aggressive,[5] and micropapillary types more extensive.[6] Growth pattern, however, often varies from one part of the tumor to another, which at least partly explains why architectural classifications are associated with a low level of observer consistency.[7] Moreover, in recent years, evidence has been produced that cytological features are more important in determining local recurrence.[8]

These considerations have stimulated a number of groups to propose new classifications of DCIS, but any new system, before being generally adopted, must have demonstrable prognostic value and consistency of application.

The aim of the current study was thus to investigate the effectiveness of four new classifications in predicting

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recurrence after local excision and compare them with the traditional method based on architecture. The consistency with which these systems can be applied will be addressed in a subsequent communication.

MATERIALS AND METHODS

Selection of Cases

Cases of DCIS were retrieved from the files of the Department of Histopathology of the Royal Marsden Hospital. The criteria for inclusion in the study were (1) unequivocal DCIS without invasive carcinoma at first presentation; (2) no relapse with ipsilateral invasive carcinoma within 6 months of first presentation; and (3) surgery only as the first line of treatment. In some cases, a second operation was done within 6 months of the primary surgery because of residual disease. These two operations were regarded as one event for the purposes of the study. Disease detected after 6 months of diagnosis was considered as recurrence and was categorized as a second event. All cases in which recurrence occurred (subjects) were identified and matched with nonrecurrent cases (controls) in a ratio of 1:2. The criteria used for matching were age at diagnosis and length of follow-up after surgery.

Using these criteria, more than 500 cases of DCIS were retrieved, of which 59 developed recurrence. Twelve were excluded because of subsequent invasive disease in the contralateral breast or because histological material was no longer available. The remaining 47 subjects were matched with 94 controls, making a total of 141 cases. It later became apparent that 17 patients had received adjuvant radiation therapy: four subjects and 13 controls. These patients were excluded from the analysis because they were not proportionately distributed between the two groups and we thought that there was a theoretical possibility that irradiation may be more effective against some histological types than others. This left 43 subjects and 81 controls.

Adequacy of local excision could not be controlled because there were insufficient data in the original histological reports, and marking ink was not generally used. This was in any case considered unnecessary in view of the study design. Because DCIS is a unicentric process, it is evident that complete excision could not have been achieved in the subjects. In predicting local recurrence, histological classifications are thus identifying lesions that are unlikely to have been completely removed and that are capable of regrowing to a clinically or radiologically detectable size.

Clinical Details

The patients' age range was from 28 to 76 years, with a median of 52 years. Median age at diagnosis for the subjects was 50 years (range, 28 to 71) and for controls 53 years (range, 30 to 76). Sixty-one percent of subjects and 65% of controls were symptomatic at presentation. The remaining patients were asymptomatic, their lesions being detected by mammography.

Treatment Details

Initial treatment for all cases was surgery alone, either localization or excision biopsy in the first instance. In 22 cases (seven subjects and 15 controls), initial biopsy was followed within 6 months by wide local excision. A further 15 cases (four subjects and 11 controls) underwent subsequent subcutaneous mastectomy.

Classification

The slides for the subjects and controls were mixed before being examined to ensure that the classifications were applied 'blind.' All cases were categorized using the following five classifications:

Architectural Classification. The DCIS was defined as *solid* when the ductular lumen was replaced by solid sheets of neoplastic cells. *Comedo* DCIS (Fig 1) was defined as a subtype of solid DCIS exhibiting a central zone of confluent necrosis. *Cribriform* DCIS (Fig 2) was characterized by the presence of secondary luminal spaces giving rise to a sieve-like appearance. *Micropapillary* DCIS exhibited finger-like papillary projections into dilated ductal spaces. The papillae generally lacked fibrovascular cores. *Intracystic papillary* DCIS was defined as a localized tumor in a dilated duct, usually close to the nipple. The papillae generally exhibited fibrovascular cores.

All architectural patterns present were recorded.

The European Pathologists Working Group (EPWG) Classification. This system was devised by a group of European Pathologists.[9] Three categories are recognized: (1) *poorly differentiated,* in which the DCIS is composed of cells with very pleomorphic, irregularly spaced nuclei, containing coarse, clumped chromatin, prominent nucleoli, and frequent mitoses. The secondary defining feature, cell polarization, is absent or only focally present. The growth pattern is usually solid but may appear to be cribriform or micropapillary. Central comedo-type necrosis is usually, but not invariably, present (Fig 1). Calcification, when present, is amorphous; (2) *Well-differentiated,* in which the cells exhibit

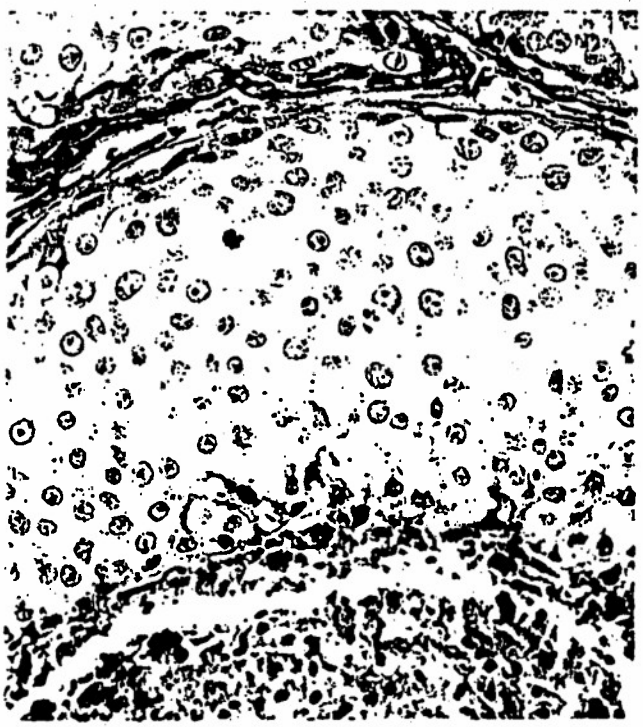

FIGURE 1. High nuclear grade (poorly differentiated, comedo) DCIS. There is pronounced pleomorphism of nuclei, which show one or more prominent nuclei. Mitoses are fairly numerous. Comedo necrosis is seen at the bottom of the picture

FIGURE 2. Low nuclear grade (well-differentiated, cribriform, without necrosis) DCIS. The nuclei are small, hyperchromatic, and uniform, and there is a clear zone of cytoplasm between the nuclei and the luminal membranes.

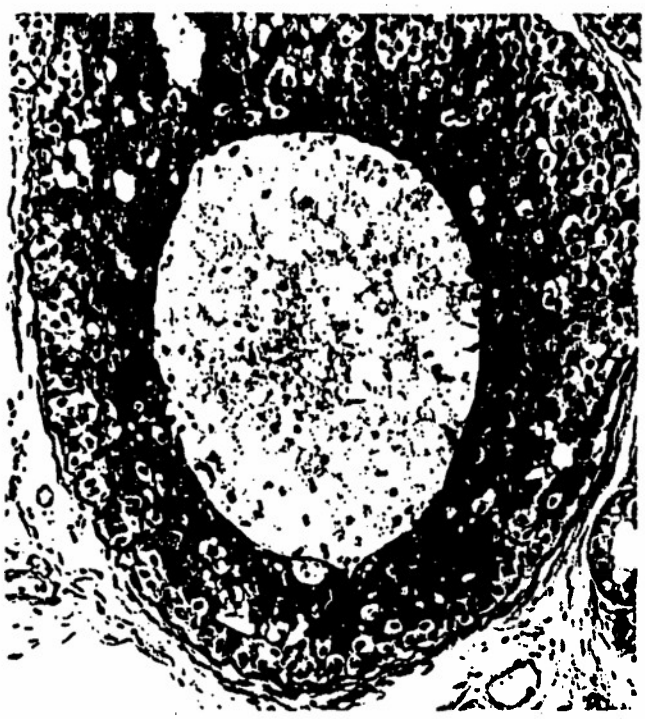

FIGURE 3. Intermediate nuclear grade (intermediately differentiated, without necrosis) DCIS. The nuclei are vesicular and fairly large, but they are uniform, and the nucleoli are small or indiscernible. Mitoses are infrequent. The cells occupying the lumen are macrophages and not necrotic cells.

monomorphic, regularly spaced nuclei fine chromatin, inconspicuous nucleoli, and few mitoses (Fig 2). The cells show polarization around secondary lumina or over papillae with orientation of their apical borders toward the lumen. The growth pattern is usually cribriform, micropapillary, or clinging, although a solid variant also occurs. Necrosis is uncommon and tends to be minimal. Calcification, when present, is usually psammomatous; (3) *intermediately differentiated,* composed of cells showing some pleomorphism but not as marked as in the poorly differentiated group (Fig 3). They show polarization (Fig 4) but this is generally less pronounced than in the well-differentiated category.

Each case was classified according to the most poorly differentiated area present.

The Classification of the United Kingdom and European Commission Breast Screening Pathology Working Groups. This classification has been adopted by the UK National Health Service Breast Screening Programme (NHSBSP) and those initiated by the European Commission (EC) under the Europe Against Cancer Programme.[10,11] It is derived from that of the EPWG. The tumors are divided into (1) *high,* (2) *intermediate,* and (3) *low nuclear grade* using exactly the same criteria, but cell polarization is not taken into account because it was thought that this criterion might not always correlate with nuclear grade and could be difficult to apply consistently. Each case was classified according to the highest nuclear grade present.

The Nottingham Classification. This classification[3] is based on the presence of necrosis. Lesions are divided into (1) *pure comedo DCIS,* in which the ducts show central lumina containing necrotic debris surrounded by large pleomorphic viable cells in solid masses (Fig 1); (2) *DCIS with necrosis,* where there are necrotic neoplastic cells within duct lumina but without a true comedo pattern (Fig 4). This group includes tumors with micropapillary or cribriform architecture exhibiting a significant amount of necrotic cellular debris; (3) *DCIS without necrosis,* where there is no evidence of necrosis in any of the tissue examined or it is limited to a few necrotic or desquamated cells in lumina.

FIGURE 4. Intermediate nuclear grade (intermediately differentiated, with necrosis) DCIS. The nuclei are vesicular and larger than those in Figure 2, but they are uniform, and the nucleoli are small or indiscernible. Mitoses are infrequent. The cells show polarization around the secondary lumina, many of which contain necrotic cells.

Each case was classified according to the worst category present.

The Van Nuys Classification. This system[12] exhibits features of the last two classifications. Lesions are first divided into high-grade and non–high-grade based on nuclear morphology and the latter subdivided into those with and without significant necrosis. There are thus three groups: (1) *high grade,* (2) *non–high grade with necrosis,* and (3) *non–high-grade without necrosis.* This classification was applied by combining our findings from the last two classifications. The criteria for identifying the high-grade cases were the same as those used in the NHSBSP Classification. The remainder were then subdivided according to whether significant necrosis was present when applying the Nottingham Classification 4).

Each case was classified according to the worst category present.

Appropriate Application of Classifications. To ensure that the classifications were applied appropriately, one of the authors (S.B.) was given the task of learning all the classifications from at least one representative of the formulators. After learning to apply them, the first 32 cases of the study were classified and sent to at least one of these representatives for verification. The kappa statistics obtained when those diagnoses were compared with those of S.P. using the Nottingham classification, R.R.M. using EPWG system, and J.P.S. using the NHSBSP/EC classification were 0.9, 0.7, and 0.6, respectively. The first two of these were regarded as satisfactory, and S.B. therefore applied both classifications to the remaining cases alone without further consultation. The last, however, was regarded as less than satisfactory, and the discrepent cases were therefore reviewed by S.B. and J.P.S. together. Having identified the causes of the inconsistencies, the remaining cases were then classified by S.B. alone.

Follow-Up Details

The median time from the initial diagnosis to disease recurrence for the 43 subjects who relapsed was 39 months (range, 7 to 125). The median length of follow-up for the controls was 68 months (range, 15 to 221). Fifty-six percent of the recurrences occurred within 4 years and 73% by 5 years. The median length of follow-up for the controls was approximately double the median interval between first event and recurrence for the subjects.

Statistical Methods

Nonparametric methods were used throughout this study. The Mann-Whitney test was used when comparing original outcomes between two groups, and the chi-squared test was employed to compare proportions. The log-rank test was used to assess differences between groups when comparing the time to recurrence. Cox's regression was used to compare the prognostic value of different grading methods by comparing the reductions in log likelihood.

RESULTS

Analysis of Classifications

Architectural Classification. The use of this system resulted in the identification of the following patterns: solid in 46, comedo in 29, cribriform in 77, micropapillary or papillary in 28. More than one pattern of growth (mixed) was identified in 47 cases. Of these, 18 with solid, nine with comedo, 27 with cribriform, and 11 with papillary growth pattern recurred. Using Cox's regression analysis to determine whether any of the growth patterns was associated with a higher probability of recurrence, no statistically significant difference was found.

The European Pathologists Working Group Classification. The distribution of the 124 cases in the three categories was: 74 poorly differentiated, 37 intermediate, and 13 well-differentiated cases. Thirty poorly differentiated, 10 intermediately differentiated, and three well-differentiated cases recurred. Figure 5 shows the probability of recurrence. Although there were differences in recurrence rates among these groups, they did not achieve statistical significance at the 5% level ($P = .08$).

The Classification of the NHSBSP/EC Working Groups. The distribution of the 124 cases in the three categories was: 77 high nuclear grade, 40 intermediate, and seven low nuclear grade. Thirty-four high, seven intermediate, and two low nuclear grade cases recurred. It can be seen from these figures that a proportion of cases regarded as well or intermediately differentiated using the EPWG classification were upgraded when cell polarization was disregarded and that some of these cases recurred. A recurring case classified as high nuclear grade using the NHSBSP/EC system and intermediately differentiated in the EPWG scheme because the cells were regarded as polarized, is illustrated in Figure 6. A statistically significant relationship between nuclear grade and recurrence was observed using this classification ($P = .009$) (Fig 7).

Nottingham Classification. The distribution of the 122 cases in the three categories was: 28 comedo, 57 with necrosis and 37 without necrosis. It was not thought appropriate to classify the two cases of papillary intracystic carcinoma using this system. Nine cases of comedo, 24 of DCIS with necrosis, and nine without necrosis recurred. Figure 8 shows that the probability of recurrence was not significantly different in the three groups ($P = .31$).

The Van Nuys Classification. The distribution of the 122 cases was 77 high-grade, 18 non–high grade with necrosis, and 27 non–high grade without necrosis. The two cases of papillary intracystic carcinoma were not classified using this system. Thirty-four high-grade, four non–high-grade with necrosis, and four non–high-grade cases without necrosis recurred. Figure 9 shows that there were significant differences in the probability of recurrence among the three groups ($P = .001$).

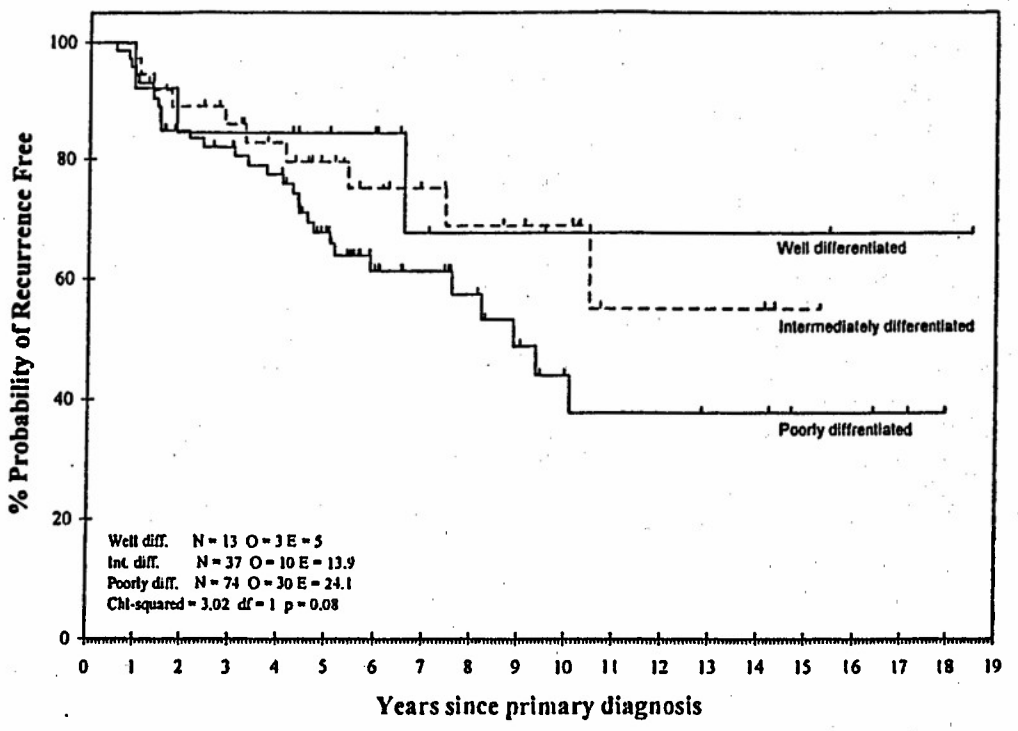

FIGURE 5. Recurrence-free survival using the EPWG classification.

Type of Recurrence

Disease type at recurrence for the 43 subjects was as follows: 28 DCIS only, 13 in situ and invasive ductal carcinoma, and two invasive ductal carcinoma only. The median time to invasive recurrence was 65 months (range, 10 to 126 months) compared with 18 months (range, 7 to 98 months) to noninvasive recurrence. There was no evidence that any particular morphological type of DCIS (using any of the classifications) was more prone to develop invasive recurrence, although the ability to detect any difference was limited by the small number of events.

Time to Recurrence

This is shown in Figures 5, 7, 8, and 9. Surprisingly, there was no clear relationship between any of the histological types and the interval between primary excision and recurrence.

DISCUSSION

Unlike its lobular counterpart, DCIS is generally a unifocal disease in which recurrences develop almost invariably at the site of previous surgery. Complete local excision is thus curative, but defining the precise limits of the process may be difficult or impossible because of extensive microscopic spread along the duct system. Pathological assessment of excision margins is consequently of limited value. The recognition that DCIS is not a single morphological entity but a spectrum of proliferations with different biological behavior has stimulated a number of groups to devise classifications that might help to predict the likelihood of recurrence after breast-conserving surgery.[3,6,8,12]

The current study was undertaken with the aim of comparing five classifications for their ability to predict outcome in a group of cases with long follow-up. Forty-seven patients who developed recurrent carcinoma were matched with twice the number of controls and their histological sections classified without knowledge of their outcome. The criteria for matching were length of follow-up and age at diagnosis, which may be an important influence on prognosis.[13,14] It was important that the controls were followed up for a length of time sufficient to maximize the possibility that recurrences occurring within a similar time frame to those seen in the subjects would have been detected. The follow-up time for the control patients was significantly longer than the time to first recurrence in the subjects. With 43 events, it is possible to detect reliably differences between groups corresponding to a threefold increase in the event rate in the poorest prognosis group relative to the good prognosis group (90% power, two-sided 5% significance level).

Cases could not, however, be matched for adequacy of local excision. To ensure long follow-up periods, it was necessary to select lesions diagnosed at a time when excision margins were not routinely assessed. As a unicentric process, however, local recurrence of DCIS is dependent on incomplete excision and the ability of the residual tumor to grow, attributes that must have been present in the study group to a greater extent than the controls. Furthermore, because the comparison of classifications was undertaken on the same group of patients, differences in clinical outcome could not have been confounded by differences between patients.

Assessing adequacy of local excision is difficult or sometimes impossible, even using combined radiological and histological techniques. Tumor may not remain

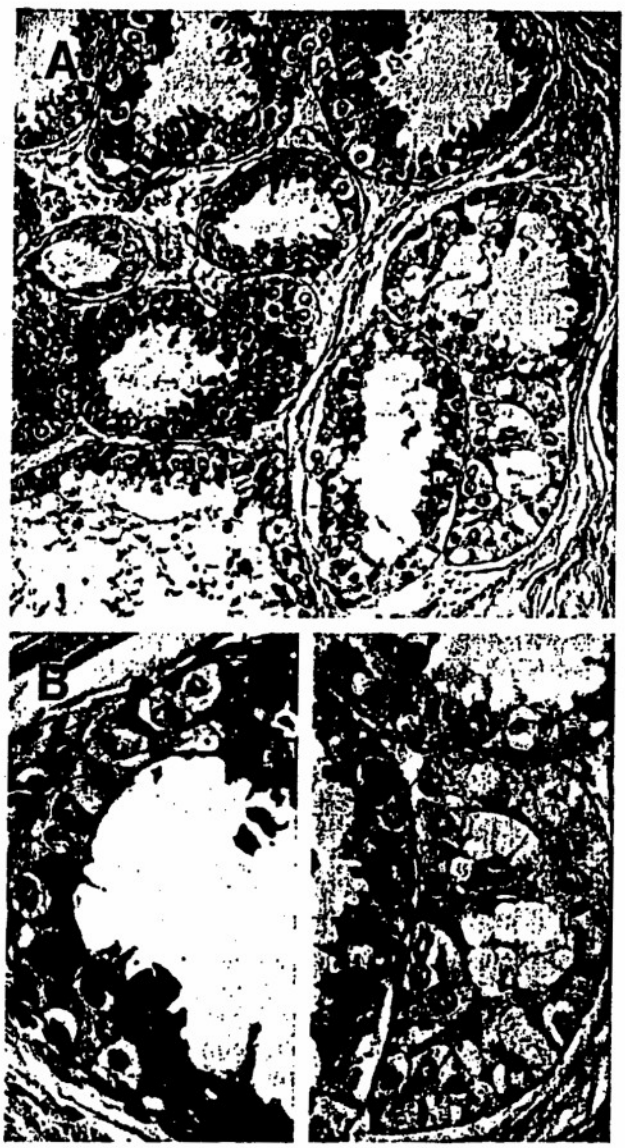

FIGURE 6. DCIS classified as high nuclear grade using the NHSBSP/EC classification but as intermediately differentiated using the EPWG system: (A) low-power view to show micropapillary/clinging growth pattern. (b) and (c) High-power views to show nuclear features and cell polarization, which was present in many parts of the lesion.

in the breast when the excision margin was reached, either because it did not actually extend beyond it or because residual disease was destroyed by the surgical procedure. Sometimes, however, reexcision specimens appear not to contain residual tumor because of sampling error, giving an erroneous impression that the lesion was originally completely excised. Conversely, a false impression of complete excision may be obtained when the relevant part of the tumor is not sampled. This is particularly likely to occur with poorly delineated lesions. Three-dimensional studies by Faverly et al,[15] however, have suggested that in some cases there may even be gaps in DCIS occupied by apparently non-neoplastic epithelium. This is more likely to occur in the well-differentiated or low nuclear grade types. It is thus possible for surgical excision to be incomplete even if normal breast epithelium is present between the DCIS and the excision margin.

Fisher et al[16] reviewed histological material from the United States National Surgical Adjuvant Breast Project and divided cases into those in which the margins were thought to be involved and those in which they were not. Margin involvement was regarded as transection of the tumor; lesions that were described as "close" or "too close" were regarded as completely excised. During a mean follow-up period of 48 months, recurrences were observed after lumpectomy alone in 11% of patients with free margins and in 25% of those where they were involved. Similar findings were obtained by Lagios et al,[17] where a recurrence rate of 10% was encountered in unirradiated patients in whom excision was considered to be complete by histological examination, radiographic-pathologic correlation, and postoperative mammography. Solin et al[18] reviewed cases from many centers and found that where DCIS extended to within 2 mm of the margin, recurrence occurred in 12% compared with 4% of those where tumor was greater than this distance away. The difference was not, however, statistically significant. In the study of Silverstein et al,[19] 26 patients with DCIS underwent reexcision of their disease. In 10, the initial biopsy had clear but close margins, and none exhibited residual tumor in the reexcision specimens. The remaining 16 patients had involved margins, but residual tumor was found in only five.

Pathological detection of margin involvement thus correlates with presence of residual DCIS in the breast and clinical recurrence, although the correlation is far from perfect because of significant technical problems in assessment. The accuracy of prediction depends on a number of factors, including the care with which the specimen is examined, the number of blocks taken, the length of time the patient is followed-up, and how adequacy of excision is defined. Based on the current study, it would seem important to assess excision margins of subcutaneous mastectomy specimens, because we observed several recurrences after this procedure.

We found no significant relationship between histology and clinical outcome using the classifications based on growth pattern or primarily on the presence of necrosis. The Nottingham classification had the advantage of being easy to learn but had two important drawbacks: (1) not all high-grade lesions were of comedo type or, indeed, even necrotic and (2) the dividing line between comedo and noncomedo necrosis was not always clear.

Statistically significant correlations were, however, observed using the system employed by the NHSBSP and EC Working Groups, which is based exclusively on nuclear grade, and the Van Nuys classification, which is based on nuclear grade and the presence of necrosis. A better correlation was seen using the latter than the former, the difference being explained by improved discrimination between the moderate and good prognostic groups using the Van Nuys method (see Figs 7 and 9). This was a somewhat surprising observation given the lack of prognostic significance of necrosis in the

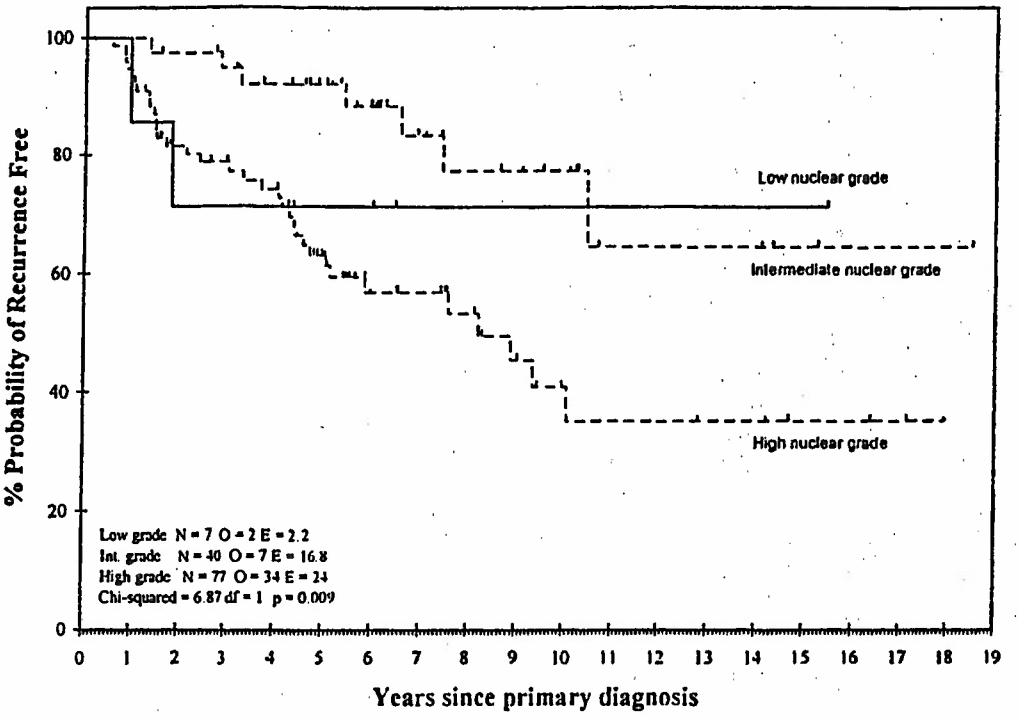

FIGURE 7. Recurrence-free survival using the NHSBSP/EC classification.

Nottingham classification, but our findings broadly confirm those of Silverstein et al,[12] who first reported the Van Nuys system.

Unexpectedly, the NHSBSP/EC system performed better than that of the EPWG from which it is derived. The EPWG classification, however, takes into account cell polarization as well as nuclear grade, and this had the effect of downgrading some cases where the nuclear grade was high or intermediate but where the cells were polarized (Fig 6). Some of these downgraded cases recurred. The different prognostic significance that we observed between these two classifications is thus based on a small number of cases. Nevertheless, on the evidence of the current study, it appears that cell polarization is much less important than nuclear grade in predicting local recurrence. A recent review of classification of DCIS[20] stresses the importance of nuclear grade as the primary feature of the EPWG classification and emphasizes that cell polarization is a secondary feature that is of most value in categorizing cases where the precise degree of nuclear differentiation is difficult to establish. Possibly, therefore, some of our cases would

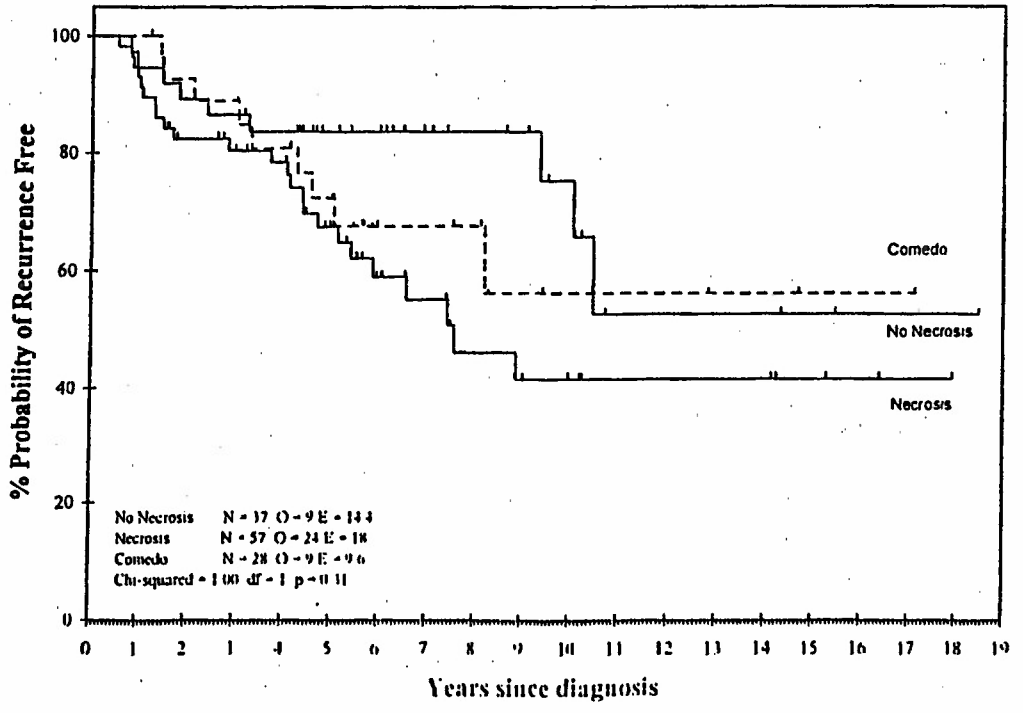

FIGURE 8. Recurrence-free survival using the Nottingham classification.

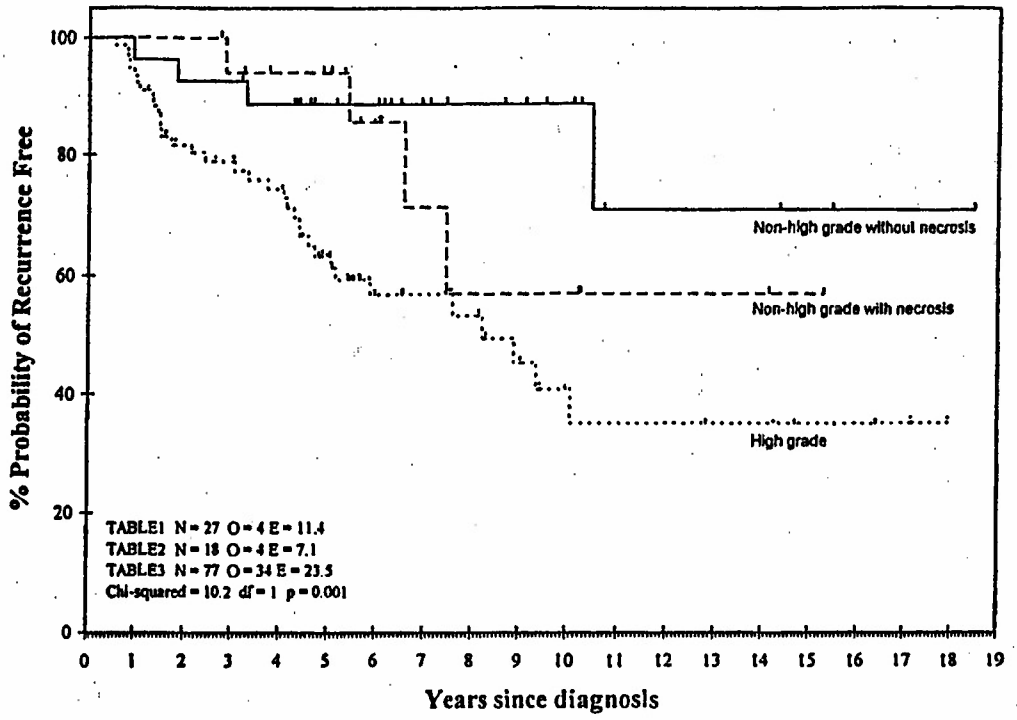

FIGURE 9. Recurrence-free survival using the Van Nuys classification.

not have been downgraded by other investigators, and this is worthy of further investigation.

Other workers have also shown the importance of nuclear grade. Lagios[8] studied recurrence after local excision in relation to this feature and growth pattern. High nuclear grade lesions recurred more frequently than those of intermediate or low grade even among tumors exhibiting similar (cribriform/papillary) architecture. Bellamy et al[6] found that high-grade DCIS was significantly more often incompletely excised compared with low-grade DCIS even though micropapillary tumours were more likely to involve multiple quadrants regardless of growth pattern. Recurrence as invasive carcinoma was more likely to follow high-grade lesions, a finding we were unable to confirm in the current study.

An advantage of the current study was the long follow-up period, which allowed us not only to determine recurrence rates but also the period over which they occurred. Intuitively, one would expect high-grade lesions to recur sooner than those of low or intermediate grade in view of their presumed faster growth rate, but in the current study, recurrences from low- and intermediate-grade cases appeared over a time course similar to that of high-grade lesions, which continued to recur over a 10-year period before the disease-free survival curves flattened out. Concerning the type of recurrence, we found no evidence that high-grade cases were more likely to recur as invasive carcinoma.

Lagios et al[17] found a relationship between lesion size and recurrence after local excision of DCIS, but this was not confirmed by Fisher et al,[16] probably because the number of tumors greater than 1 cm in the latter study was relatively small. The degree of circumscription of the tumor is also likely to be important, because circumscribed tumors are easier to excise; circumscription may, however, be difficult to evaluate.

It is likely that the most accurate prognostication will be achieved by combining several features related to recurrence. Recently, Silverstein et al[21] devised an index based on tumor size, margin width, and the Van Nuys classification, each receiving a score of 1 to 3. For size, a score of 1 was given for tumors 15 mm or less in diameter, 2 for those 16 to 40 mm, and 3 for those larger than 40 mm. For excision margins, a score of 1 was given where the tumor-free margin exceeded 10 mm, 2 where it was 1 to 9 mm, and 3 where it was less than 1 mm. Using the Van Nuys classification, a score of 1 was given for non–high nuclear-grade lesions without comedo-type necrosis, 2 for non–high nuclear grade with comedo-type necrosis, and 3 for high-nuclear-grade lesions with or without comedo-type necrosis. Cases were then divided into three groups with aggregate scores of 3 to 4, 5 to 7, and 8 to 9. Recurrence-free survival was predicted more accurately by the index than by any of the three constituent pathological variables alone. Furthermore, it was found that patients with prognostic index scores of 3 to 4 did not show a local disease-free survival benefit from breast irradiation, whereas those with scores 5 to 7 benefited significantly from adjuvant radiation therapy. Although patients with scores of 8 to 9 also benefitted from irradiation, the recurrence rates after local excision were extremely high even where radiation therapy was given, suggesting that mastectomy is most appropriate for these patients. These important findings are in need of independent validation.

A crucial aspect of any pathological classification is the consistency with which it can be applied. A limited consistency analysis was undertaken in the current study but this was simply to determine the degree with which

the first author agreed with some of the formulators to ensure that the classifications were applied appropriately. A formal statistical analysis involving a large number of pathologists' observations is underway.

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07.01.94 - 30.06.95	Registrar in Histopathology, Royal Marsden Hospital, London.
04.01.90 - 06.31.94	Registrar in Histopathology, St.George's Hospital Medical School & St. Helier's Hospital, London.
12.27.89 - 03.31.90	Locum Registrar, Barnet General Hospital, London.
10.01.89 - 12.24.89	Observor in Academic Haematology & Histopathology, Royal Marsden Hospital, London.
04.01.87 - 09.27.89	Lecturer in Histopathology, Grant Medical College, Bombay.
03.01.86 - 01.31.87	Registrar in Histopathology, Tata Memorial Hospital, Bombay.
03.01.84 - 02.28.86	Resident Pathologist, J.J. Group of Hospitals, Bombay.
01.01.83 - 12.31.83	Rotating internship, J.J. Group of Hospitals, Bombay.

QUALIFICATIONS

1999	Board Eligible (AP/CP)	American College of Pathologists
1993	MRCPath(Histopath)	Royal College of Pathologists, London, U.K.
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1982	M.C.P.S.	College of Physicians and Surgeons, Bombay, India
1982	M.B.B.S.	Bombay University, India (Grant Medical College)

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Travel Grant, Association of Clinical Pathologists, 1994

LICENSES

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ECFMG No. 0-510-443-5

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DISSERTATION AT M.D.

Fine needle aspiration cytology of the breast. Correlation with histology.

INVITED LECTURES AND TALKS

Invited Lecture, "Interpretation of Upper Gastro-Intestinal Endoscopic Biopsies" - Indian Association of Pathologists, Maharashtra Chapter, 1998.

Invited Lecture, "Upper GI endoscopic biopsies" - Tata Memorial Hospital for Cancer, Bombay, 1998.

"Anti-alpha-1 microglobulin antibodies are an important tool in the differential diagnosis of liver tumors" - Chairman's Retreat. Albert Einstein College of Medicine, 1998.

"Alpha-1 microglobulin - a new immunohistochemical marker for liver tumors" - Young Investigators Night, Albert Einstein College of Medicine, 1998.

"Alpha-1 microglobulin in health and disease" - Clinical Pathology Lecture Series, Jacobi Medical Center, 1998.

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ABSTRACTS

Submitted for USCAP/IAP '99

Badve S, Soundarajan S, Cooperman A, Mahadevia P. Unusual causes of benign obstructive pancreato-biliary disease leading to pancreato-biliary resection..

Logdberg L, **Badve S**, Greco MA, Garcia de Davila MT, Mitsudo S. Alpha-1 microglobulin expression by hepatoblastomas.

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